International Journal of Drug Delivery 3 (2011) 546-557

http://www.arjournals.org/index.php/ijdd/index

Review Article

ISSN: 0975-0215

Nanosuspensions: The Solution to Deliver Hydrophobic Drugs

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Abstract

Most of the drugs are not soluble in water and they create major problem during formulation they also show poor bioavailability. Reduction in particle size of such drugs enhances the dissolution rate and bioavailability. Nano suspension a promising delivery used to enhance the solubility of hydrophobic drugs. Media milling and high pressure homogenization technique are used commercially to produce nano suspensions. Recently emulsion and micro emulsion as templates are used to produce nano suspension. They are administered by Parenteral, per oral, ocular and pulmonary routes. Now their application also extended to site specific delivery. This review describes the methods of pharmaceutical nanosuspension production, formulations and pharmaceutical applications in drug delivery as well as the marketed products. Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion.

Keywords: Nanosuspensions, Hydrophobic drugs, nanospheres, drug delivery

Introduction

The formulation of poorly water soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmes are poorly water-soluble[1]. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is too low bioavailability and/or erratic absorption[2]. The problem is even more intense for drugs such as itraconazole and carbamazepine (belonging to Biopharmaceutical Classification Scheme Class II (BCS CLASS II)) as classified by BCS System[3,4] as they are poorly soluble in both aqueous and organic media, and for those drugs having a log P value of 2. The performance of these drugs is dissolution rate-limited (for Class II and III drugs) and is affected by the fed/fasted state of the patient. Dissolution rates of sparingly soluble drugs are related to the shape as well as the particle size. Therefore decrease in particle size results in an increase in dissolution rate[5]. There are number of formulation approaches that can be used to resolve the problems associated with the low solubility and low bioavailability of these class II drugs. Some of the approaches to increase solubility include micronization, solubilisation using co-solvents, use of permeation enhancers, oily solutions, surfactant dispersions[6], salt formation[7] and precipitation techniques[8,9]. Most of these techniques for solubility enhancement have advantages as well as some limitations and hence have limited utility in solubility enhancement. Other techniques used for solubility enhancement like microspheres, emulsions, microemulsions[10], liposomes[11], super critical processing, solid-dispersions[12] and inclusion complexes using cyclodextrins[13] show reasonable success but they lack in universal applicability to all drugs. These techniques are not applicable to the drugs, which are not soluble in both aqueous and organic media. However, there still remains an unmet need to equip the pharmaceutical industry with particle engineering technologies capable of formulating the poorly soluble drugs to improve their efficacy and to optimize therapy with respect to pharmacoeconomics. Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water-and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies. This review focuses on the various aspects of nanosuspensions and their potentials as promising strategy in drug delivery. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} meters[14]. Nanotechnology and nanoscience are widely seen as having a great potential to bring benefit to vast areas of research and applications. Nanodevices are somewhere 100 to 10000 times smaller human cells. They are similar in size to large

biological molecules such as enzymes and receptors. This offers the unprecedented and paradigm changing oppurtunity to study and interact with normal as well as cancer cells at the molecular and cellular level scales and during the earliest stages of the cancer process. Nanoscale device can readily interact with biomolecules on both the surfaces of cells & inside of cells. Nanogen develops this technology. Nanogens technology utilizes the natural (+ve) or (-ve) charge of most biological molecules[15].

Nanoparticles

Nanoparticles are solid polymeric, submicronic colloidal systems that range between 5-300nm consisting of macromolecular substances that vary in size 10nm to 100nm. The drug of interest is dissolved, entrapped adsorbed, attached or encapsulated into the nanoparticle matrix[16]. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes[17,18]. The advantages of using nanoparticles for nanoparticles loaded with drugs because of their small size can penetrate through small capillaries and are taken up by cells and allow the drug release at right rate and dose at specific sites in the body for a certain time to release the accurate delivery, which enhances the therapeutic effect and reduces the toxicity and side effects. The use of biodegradable materials for nanoparticles preparation allows sustained release within the target site over a period of days or even weeks. In spite of these advantages, nanoparticles do have limitations. For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available. The cytotoxicity of polymers and the lack of a suitable large scale production are the drawbacks of polymeric nanoparticles. To overcome these drawbacks, solid lipid nanoparticles are preferred.

Solid lipid nanoparticles

Solid lipoid nanoparticles are one of the novel potential colloidal carriers[19] in the range of 100-150nm as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid [20]. They have many advantages such as good biocompatibility, low toxicity and lipophillic drugs are better delivered by solid lipid nanoparticles and the system is physically stable. Solid lipid nanoparticles may be a promising sustained release and drug targeting system for lipophilic CNS antitumor drugs[16].

Drug Nanocrystals

Drug nanocrystals are pure solid drug particles with a mean diameter below 1000 nm. The term drug nanocrystals implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals have to be distinguished from polymeric nanoparticles[21], which consist of a polymeric matrix and an incorporated drug. Drug nanocrystals do not consist of any matrix material.

Nanosuspensions

Nanosuspensions are sub-micron colloidal dispersions of nanosized drug particles stabilized by surfactants[22]. Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion[23]. These can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. Nanosuspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption. Apart from this, nanosuspensions have some following advantages: Firstly, drugs no longer need to be in the soluble form. It is effective for those molecules insoluble in oils. Secondly, the high drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose. Thirdly, nanosuspensions can increase the physical and chemical stability of drugs as they are actually in the solid state. Finally, nanosuspensions can provide the passive targeting [24].

Preparation Methods of Nanosuspensions

Preparation of nanosuspensions are reported to be more cost effective and technically more simpler alternative than liposomes and other conventional colloidal drug carriers, particularly for poorly soluble drugs and yield a physically more stable product. The principle techniques used in recent years for preparing nanosuspensions can be classified into four basic methods: (a) Homogenization (b) Wet milling (c) Emulsification-solvent evaporation and (d) Precipitation or micro precipitation method. Nanosuspension engineeringprocesses currently used are preparation by precipitation, high pressure homogenization, emulsion and milling techniques[25]. For the nanosuspensions manufacture, there are two converse methods -'bottom-up' and the 'topdown' technologies[26]. The bottom-up technology is an assembling method from molecules to nanosized particles, including microprecipitation, microemulsion, melt emulsification method and so on. The top down technology is a disintegration approach from large particles, microparticles to nanoparticles, such as high-pressure homogenization and media milling method.

The 'Top Down Technologies' are the disintegration methods and are preferred over the precipitation methods. These include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege). Few other techniques used for preparing nanosuspensions are emulsion as templates and microemulsion as templates.

Media milling

Media milling is a further technique used to prepare nanosuspensions[27,28]. This patent-protected technology is acquired by Elan Drug Delivery[29]. In this technique, the nanosuspensions are produced using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. The drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generate as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. The milling medium is usually composed of glass, zirconium oxide or highly cross-linked polystyrene resin. In batch mode, the time required to obtain dispersions with unimodal distribution profiles and mean diameters <200nm is 30–60 min. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then milling media or pearls are rotated at a very high shear rate. Drugs like cilostazol[30], danazol and naproxen. In nanosuspensions, the particles are charged with polymeric media. The mill can be operated in a batch or recirculation mode. Slurry consisting of drug, water and stabilizer is fed into the milling chamber and processed into nanocrystalline dispersion.

Principle

The high energy and shear forces generate as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide or highly cross-linked
polystyrene resin. The process can be performed in either batch or recirculation mode. In batch mode, the time required to obtain dispersions with unimodal distribution profiles and mean diameters<200nm is 30–60 min. The media milling process can successfully process micronized and non-micronized drug crystals. Once the formulation and the process are optimized, very little batch-to-batch variation is observed in the quality of the dispersion.

Advantages

(1). Very dilute as well as highly concentrated nnanosuspensions can be prepared by handling 1 mg/ml to 400 mg/ml drug quantity.
(2) Nanosized distribution of final nanosized product

Disadvantages

1. The media milling technique is time consuming.
2. Some fractions of particles are in the micrometer range.
3. Scale up is not easy due to mill size and weight.

Dry Co-Grinding

Recently, nanosuspensions are obtained by dry milling techniques. Successful work is reported in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media[31]. Itoh *et al*[32] reported that the colloidal particles formation of many poorly water soluble drugs like griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS). Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives are used[33]. Physicochemical properties and dissolution of poorly water soluble drugs are improved by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug[34]. Dry co-grinding can be carried out easily and economically and can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable. Clarithromycin[34] and Glibenclamide[35] nanosuspensions are prepared by this method.

Advantages

(1) Easy process and no organic solvent required.
(2) Require short grinding time.

Disadvantages

Generation of residue of milling media.

High pressure homogenization

It is the most widely used method for the preparation of the nanosuspensions of many poorly water soluble drugs[36,37]. Different methods are developed based on this principle for preparation of nanosuspensions are Dissocubes, Nanopure, Nanoedge, Nanojet technology. In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer.

Principle

During homogenization, the fraction of drug particles is brought about by cavitation, high-shear forces and the collision of the particles against each other. The drug suspension, contained in a cylinder of diameter about 3 mm, passes suddenly through a very narrow homogenization gap of 25µm, which leads to a high streaming velocity. In the homogenization gap, according to Bernoulli's equation, the dynamic pressure of the fluid increases

with the simultaneous decrease in static pressure below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature, leading to the formation of gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached again. The implosion forces are sufficiently high to break down the drug microparticles into nanoparticles. Additionally, the collision of the particles at high speed helps to achieve the nano-sizing of the drug. To improve the efficiency of nano-sizing, the addition of viscosity enhancers is advantageous in certain cases as increasing the viscosity increases the powder density within the dispersion zone (homogenization gap). As the homogenizer can handle varying pressures, ranging from 100 to 1500 bars, the effect of the homogenization pressure on the particle size should be investigated in each case in order to optimize the process parameters. It is expected that the higher the homogenization pressure, the lower the particle size obtained. Drugs like Albendazole, Azithromycin, Fenofibrate nanosuspensions are prepared by this method,

Advantages

1. Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions.
2. Ease of scale-up and little batch-to-batch variation[38].
3. Narrow size distribution of the nanoparticulate drug present in the final product[39]

Disadvantages

1. Prerequisite of suspension formation using high-speed mixers before subjecting it to homogenization.
2. High number of homogenization cycles.
3. Possible contamination could occur from metal ions coming off from the walls.

Precipitation

Precipitation has been applied for years to prepare submicron particles within the last decade [40,41], especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in a solvent. Then this solution is mixed with a miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually water) leads to sudden supersaturation of drug in the mixed solution and generation of ultrafine crystalline or amorphous drug solids. This process involves two phases: nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate but low growth rate is necessary. Both rates are dependent on temperature: the optimum temperature for nucleation might lie below that for crystal growth, which permits temperature optimization[42]. Carbamazepine[43], Cyclosporine[44], Griseofulvin[45] nanosuspensions are prepared by this method.

Advantages

Simple process, Ease of scale up and Economical production.

Disadvantages

Growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent.

Emulsions as templates

Apart from the use of emulsions as a drug delivery vehicle, they can also be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drug nanosuspensions by the emulsification method.

In the first method, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride and chloroform were used[46].

Another method makes use of partially water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phase instead of hazardous solvents[47]. The emulsion is formed by the conventional method and the drug nanosuspension is obtained by just diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the internal phase into the external phase, leading to instantaneous formation of a nanosuspension. The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, if all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension.

Advantages

1. Use of specialized equipment is not necessary.
2. Particle size can easily be controlled by controlling the size of the emulsion droplet.
3. Ease of scale-up if formulation is optimized properly.

Disadvantages

1. Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
2. Safety concerns because of the use of hazardous solvents in the process.

3. Need for diultrafiltration for purification of the drug nanosuspension, which may render the process costly.

Microemulsions as templates

Microemulsions are thermodynamically stable and isotropically,clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant and co-surfactant [48]. Their advantages, such as high drug solubilization, long shelf-life and ease
of manufacture, make them an ideal drug delivery vehicle. There are several research papers available that describe the use of microemulsions as drug delivery vehicles[40-52].
Recently, the use of microemulsions as templates for the production of solid lipid nanoparticles[53] and polymeric nanoparticles[54] is described. Breviscapine[55] nanosuspensions are prepared by this method. The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug by intimate mixing. The suitable dilution of the microemulsion yields the drug nanosuspension by the mechanism described earlier. The influence of the amount and ratio of surfactant to co-surfactant on the uptake of internal phase and on the globule size of the microemulsion should be investigated and optimized in order to achieve the desired drug loading. The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, if all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension.

Advantages

High drug solubilisation, Long shelf life and Ease of manufacture.

Disadvantages

Use of high amount of surfactant and stabilizers and Use of hazardous solvent in production.

Formulation considerations

Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening[56] and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable nanosuspension. The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable nanosuspension.

Organic solvents

Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin,
propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially water miscible organic solvents can be used as the internal phase of the microemulsion when the nanosuspensions are to be produced using a microemulsion as a template.

Co-surfactants

The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactants can greatly influence phase behaviour, the effect of
co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.

Other additives

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.

Post-production processing

Post-production processing of nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when the best possible stabilizer is not able to stabilize the nanosuspension for a longer period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as lyophillization or spray drying may be employed to produce a dry powder of nano-

sized drug particles. Rational selection has to be made in these unit operations considering the drug properties and economic aspects. Generally, spray drying is more economical and convenient than lyophillization. The effect of post-production processing on the particle size of the nanosuspension and moisture content of dried nanosized drug should be given due consideration.

Advantages of nanosuspensions

Increase in the dissolution velocity and saturation solubility of the drug

The reason of nanosuspensions being a promising drug delivery strategy behind the increase in the dissolution velocity and saturation solubility of the nanosuspensions can be given as follows. According to the Nernst–Brunner and Levich modification of the Noyes Whitney dissolution model equation[57], the dissolution velocity of the nanosuspension increases due to a dramatic increase in the surface area of the drug particles from microns to particles of nanometer size:

$$dX/dt = ((DxA)/h)\ (CsxX/V)$$

dX/dt - dissolution velocity, D - diffusion coefficient, A - surface area of the particle, h - diffusional distance, Cs - saturation solubility of the drug, X - concentration in the surrounding liquid and V - volume of the dissolution medium.

Improved biological performance

An increase in the dissolution velocity and saturation solubility of a drug leads to an improvement in the invivo performance of the drug irrespective of the route used. The advantages related to various routes are discussed later in detail.

Ease of manufacture and scale-up

Unlike nanoparticulate carriers such as polymeric nanoparticles, which were investigated earlier, nanosuspensions are easy to manufacture. The production processes described earlier are easily scaled up for commercial production. The introduction of nanosuspension products such as Rapamune and the NanoCrystal colloidal ketoprofen is sufficient to substantiate this

Long-term physical stability

Another special feature of nanosuspensions is the absence of Ostwald ripening, which is suggestive of their long-term physical stability[58]. Ostwald ripening is described for ultrafine dispersed systems and is responsible for crystal growth and subsequently formation of microparticles. Ostwald ripening is caused by the differences in dissolution pressure/saturation solubility between small and large particles. It is in practice an effect based on the higher saturation solubility of very small particles as compared to larger ones. Molecules diffuse from the higher concentrated area around small particles (higher saturation solubility) to areas around larger particles possessing a lower drug concentration.
This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles. The diffusion process of the drug from the small particles to the large particles leaves an area around the small particles that is not saturated any more, consequently leading to dissolution of the drug from the small particles. Finally there is complete disappearance of the small particles. The lack of Ostwald ripening in nanosuspensions is attributed to their uniform particle size, which is created by various manufacturing processes. The absence of particles with large differences in their size in nanosuspensions prevents the existence of the different saturation solubilities and concentration gradients in the vicinity of differently sized particles, which in turn prevents the Ostwald ripening effect.

Versatility

The flexibility offered in the modification of surface properties and particle size, and ease of post-production processing of nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories and hydrogels, for various routes of administration, thus proving their versatility.

Characterization of nanosuspensions

Mean particle size and particle size distribution

The mean particle size and the span of particle size distribution (polydispersity index, PI) are two important characteristic parameters because they affect the saturation solubility, dissolution rate, physical stability, even in-vivo behavior of nanosuspensions. It is indicated by Muller & Peters (1998) that saturation solubility and dissolution velocity show considerable variation with the changing, particle size of the drug[59]. Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity and physical stability. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1– 0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. The coulter-counter gives the absolute number of particles per volume unit for the different size classes, and it is a more efficient and appropriate technique than LD for quantifying the contamination of nanosuspensions by microparticulate drugs.

Surface charge (zeta potential)

Zeta potential gives certain information about the surface charge properties and further the long-term physical stability of the nanosuspensions.The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself . For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient.

Crystalline state and particle morphology

The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high-pressure homogenization The changes in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis[60,61] and supplemented by differential scanning calorimetry[62]. In order to get an actual idea of particle morphology, scanning electron microscopy is preferred.

Saturation solubility and dissolution velocity

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs. The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behavior of the formulation

In vivo evaluation

The *in vivo* evaluation of the nanosuspensions is specific to drug and route of administration. The parameters which are generally evaluated *in vivo* are

1. Surface hydrophilicity/hydrophobicity (determines interaction with cells prior to phagocytosis)
2. Adhesion properties

Applications of nanosuspensions in drug delivery

Oral drug delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly. Orally administered antibiotics such as atovaquone and bupravaquone reflect this problemvery well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The amelioration in oral bioavailability can be attributed to the adhesiveness of the drug nanosuspension, increased surface area (due to reduction in particle size by 10–50-fold), increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body. Amphotericin B, a highly effective polyene antibiotic used for systemic mycoses and leishmaniasis lacks oral bioavailability. However, oral administration of amphotericin B as a nanosuspension produced a substantial improvement in its oral absorption in comparison to orally administered conventional commercial formulations such as Fungizone, AmBisome and micronized amphotericin B[62]. Nanosuspensions are also advantageous in achieving quick onset of action for drugs that are completely but slowly absorbed, i.e. those having high tmax values. This is illustrated by the study carried out for naproxen, a nonsteroidal anti-inflammatory drug. A dosage form with fast onset of action would be highly desirable for naproxen[63].

Ophthalmic drug delivery

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. One example of a nanosuspension intended for ophathamic controlled delivery was developed as a polymeric nanosuspension of ibuprofen[64]. This nanosuspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone enhance rate, drug absorption and increase the duration of drug action[65].

Pulmonary drug delivery

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Basically the nanosuspensions can be used in all nebulizers. The dispersions can be relatively high concentrated. Due to the presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery[66]. A good relationship was obtained between increasing the drug concentration in the formulation and the number of micrograms of drug delivered per actuation. In addition, bupravaquone nanosuspensions were formulated for treatment of lung infections by using nebulisation[67].

Parenteral administration

Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitonal to intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 μm to avoid capillary blockage. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspensions revealed their superiority over taxol in reducing the median tumour burden[68]. Similarly, aphidicolin, a poorly water soluble new anti-parasitic lead molecule, when administered as a nanosuspension resulted in an improvement in EC50 in comparison to DMSO-dissolved drug[69]. Rainbow and co-workers reported an intravenous itraconazole nanosuspension enhanced efficacy of antifungal activity relative to a solution formulation in rats[70].

Target drug delivery

Nanosuspensions can also be used for targeted delivery as their surface properties and in vivo behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone[71].

Topical formulations

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin[72,73].

Conclusion

The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption and bioavailability. Nanosuspension formulations are promising candidates for enhancing the solubility of poorly water soluble drugs. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, and can be used for parenteral products. To take advantage of nanosuspension drug delivery, simple formation technologies and variety applications, nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future. Production techniques such as media milling and high-pressure homogenization have been successfully employed for large-scale production of nanosuspensions. The advances in production methodologies using emulsions or microemulsions as templates have provided still simpler approaches for production but with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of nanosuspensions for various routes.

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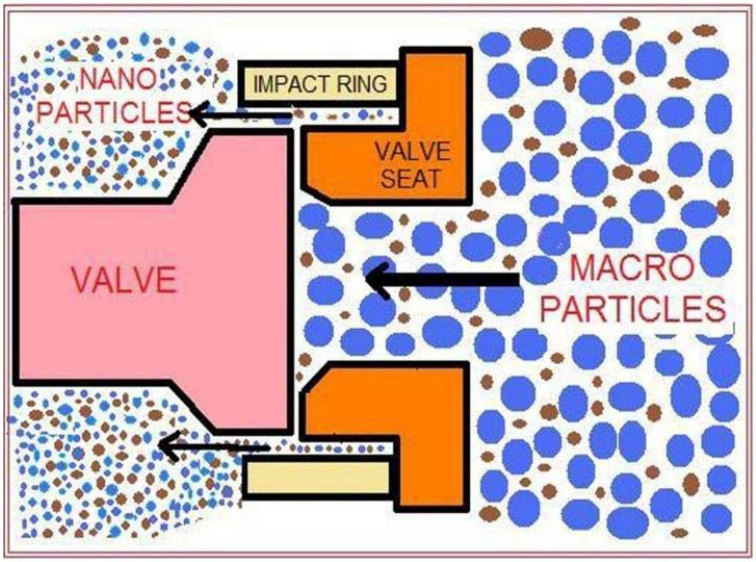

Figure 1: Schematic cartoon of the high-pressure homogenization process

Table:1.0 Current marketed pharmaceutical products utilizing nanocrystalline formation.

Product	compound name	company name
RAPAMUNE®	Sirolimus	Wyeth
EMEND®	Aprepitant	Merck
TriCor®	Fenofibrate	Abbott
MEGACE® ES	Megestrol acetate	PAR pharmaceutical
Triglide™	Fenofibrate	First Horizon pharma

Table: 2.0 Potential benefits of nanosuspension technology

Route of administration	Potential benfits
Oral	Rapid dissolution and high bioavailability
Intravenous (I.V)	Tissue targeting Rapid dissolution Longer duration of retention in systemic circulation
Occular	High bioavailability Lesser irritation
Subcutaneous/intramuscular	High bioavailability Rapid onset of action